09/836035

(FILE 'HOME' ENTERED AT 16:26:08 ON 03 JUL 2001)

FILE 'MEDLINE' ENTERED AT 16:26:16 ON 03 JUL 2001

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L1         11999 S QUINOLIN?
L2            69 S L1 (P) QUINOLON?
L3            23 S L2 AND METABOL?
L4            12 S L2 (P) METABOL?

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L4 ANSWER 1 OF 12 MEDLINE
AN 97374070 MEDLINE
DN 97374070 PubMed ID: 9230527
TI N-omega-carbethoxypentyl-4-quinolones: a new class of leukotriene biosynthesis inhibitors.
AU Desideri N; Sestili I; Stein M L; Manarini S; Dell'Elba G; Cerletti C
CS Dipartimento di Studi farmaceutici, Universita La Sapienza di Roma, Italy.
SO ARCHIV DER PHARMAZIE, (1997 Apr) 330 (4) 100-6.
Journal code: 8AC; 0330167. ISSN: 0365-6233.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199708
ED Entered STN: 19970902
Last Updated on STN: 19970902
Entered Medline: 19970818
AB 6-[(4-**Quinolinyl**)oxy]hexanoic acids and the corresponding esters were designed and synthesized as inhibitors of the production of arachidonic acid **metabolites**. The inhibitory activities were assayed in vitro by evaluation of serum leukotriene B4 and thromboxane B2 production. While all 6-[(4-**quinolinyl**)oxy]hexanoic acids and their esters proved to be inactive, the N-alkyl-4-**quinolones**, obtained as by-products in their synthesis, were found to be a new class of leukotriene biosynthesis inhibitors.
AB 6-[(4-**Quinolinyl**)oxy]hexanoic acids and the corresponding esters were designed and synthesized as inhibitors of the production of arachidonic acid **metabolites**. The inhibitory activities were assayed in vitro by evaluation of serum leukotriene B4 and thromboxane B2 production. While all 6-[(4-**quinolinyl**)oxy]hexanoic acids and their esters proved to be inactive, the N-alkyl-4-**quinolones**, obtained as by-products in their synthesis, were found to be a new class of leukotriene biosynthesis inhibitors.

L4 ANSWER 2 OF 12 MEDLINE
AN 97259447 MEDLINE
DN 97259447 PubMed ID: 9105548
TI Pharmacokinetics of prulifloxacin. 3rd communication: metabolism in rats, dogs and monkeys.
AU Okuyama Y; Morino A
CS Research Laboratories, Nippon Shinyaku Co., Ltd., Kyoto, Japan.
SO ARZNEIMITTEL-FORSCHUNG, (1997 Mar) 47 (3) 293-8.
Journal code: 91U; 0372660. ISSN: 0004-4172.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199707
ED Entered STN: 19970721
Last Updated on STN: 19970721
Entered Medline: 19970707
AB The **metabolism** of the new **quinolone** antibacterial prodrug prulifloxacin ((+/-)-6-fluoro-1-methyl-7-[4-(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl-1-piperazinyl]-4-oxo-4H-[1,3]thiazeto [3,2-a] **quinoline**-3-carboxylic acid. CAS 123447-62-1, NM441) in rats, dogs

and monkeys was investigated after oral administration of 14C-NM441 or unlabeled NM441. 1. NM394 (which is the active **metabolite** of NM441), the NM394 acyl glucuronide, the ethylenediamino form, the diol form and the amino form were found in the urine of all three species, and the oxo form was detected in monkey urine only. 2. NM394 was the main **metabolite** in the urine of dogs and monkeys. 3. NM394 was the main **metabolite** in the plasma, urine and feces in rats and NM394 and its acyl glucuronide were the main biliary **metabolites**. 4. These results indicate that NM441 was transformed into a variety of **metabolites**, but that most of the drug administered was **metabolized** to NM394 by hydrolytic cleavage of the dioxelene ring.

AB The **metabolism** of the new **quinolone** antibacterial prodrug prulifloxacin ((+/-)-6-fluoro-1-methyl-7-[4-(5-methyl-2-oxo-1, 3-dioxolen-4-yl)methyl-1-piperazinyl]-4-oxo-4H-[1,3]thiazeto [3,2-a] **quinoline**-3-carboxylic acid. CAS 123447-62-1, NM441) in rats, dogs and monkeys was investigated after oral administration of 14C-NM441 or unlabeled NM441. 1. NM394 (which is the active **metabolite** of NM441), the NM394 acyl glucuronide, the ethylenediamino form, the diol form and the amino form were found in the. . . urine of all three species, and the oxo form was detected in monkey urine only. 2. NM394 was the main **metabolite** in the urine of dogs and monkeys. 3. NM394 was the main **metabolite** in the plasma, urine and feces in rats and NM394 and its acyl glucuronide were the main biliary **metabolites**. 4. These results indicate that NM441 was transformed into a variety of **metabolites**, but that most of the drug administered was **metabolized** to NM394 by hydrolytic cleavage of the dioxelene ring.

L4 ANSWER 3 OF 12 MEDLINE
AN 97259446 MEDLINE
DN 97259446 PubMed ID: 9105547
TI Pharmacokinetics of prulifloxacin. 2nd communication: pharmacokinetics and
effect on hepatic drug-metabolizing enzyme activities after repeated administration and transfer into fetus and milk after a single administration in rats.
AU Okuyama Y; Momota K; Morino A
CS Research Laboratories, Nippon Shinyaku Co., Ltd., Kyoto, Japan.
SO ARZNEIMITTEL-FORSCHUNG, (1997 Mar) 47 (3) 285-92.
Journal code: 91U; 0372660. ISSN: 0004-4172.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199707
ED Entered STN: 19970721
Last Updated on STN: 19970721
Entered Medline: 19970707
AB Prulifloxacin ((+/-)-6-fluoro-1-methyl-7-[4-(5-methyl-2-oxo-1,3-dioxolen-4-yl) methyl-1-piperazinyl]-4-oxo-4H-[1,3]thiazeto[3,2-a]**quinoline**-3-car boxylic acid, CAS 123447-62-1, NM441) is a prodrug of a new **quinolone** carboxylic acid antibacterial agent, NM394 (CAS 112984-60-8). The pharmacokinetics of radioactivity after repeated oral administration of 14C-NM441, the effects of NM441 on hepatic drug-**metabolizing** enzyme activities after repeated oral administration

of NM441, and the transfer of radioactivity into the fetus and milk after a single oral administration of 14C-NM441 were investigated in rats. 1. The plasma concentration of radioactivity 6 h after each oral dose of 14C-NM441 (20 mg/kg) to male rats once a day for 21 days was almost constant. There was no marked difference in the plasma concentration-time curves for radioactivity after the single, 7th, 14th or 21st administration. The averaged cumulative urinary and fecal excretion of radioactivity during repeated administration did not differ from the corresponding values after a single administration. The concentration of radioactivity 8 h after each dose had reached a plateau in most tissues by the 14th administration. After the 21st dose, the radioactivity concentration in most tissues decreased along with the plasma concentration, whereas a slower elimination was observed in the skin and bone. 2. Repeated oral administration of 20 or 200 mg/kg of NM441 to male rats did not affect hepatic drug-**metabolizing** enzyme activities. 3. In pregnant rats, the maximum concentration of radioactivity in the fetus was lower than that in the maternal plasma. Furthermore, the total amount of radioactivity in the fetus was only 0.01% of the dose at 0.5 h. 4. In lactating rats, the concentration of radioactivity in the milk was substantially higher than in the plasma. 5. In conclusion, repeated administration of NM441 did not alter its pharmacokinetics, and no evidence was found that it accumulated in the body. Furthermore, there was little placental transfer. These characteristics add to the suitability of NM441 as an effective prodrug of NM394.

AB Prulifloxacin ((+/-)-6-fluoro-1-methyl-7-[4-(5-methyl-2-oxo-1,3-dioxolen-4-yl) methyl-1-piperazinyl]-4-oxo-4H-[1,3]thiazeto[3,2-a]**quinoline**-3-car boxylic acid, CAS 123447-62-1, NM441) is a prodrug of a new **quinolone** carboxylic acid antibacterial agent, NM394 (CAS 112984-60-8). The pharmacokinetics of radioactivity after repeated oral administration of 14C-NM441, the effects of NM441 on hepatic drug-**metabolizing** enzyme activities after repeated oral administration of NM441, and the transfer of radioactivity into the fetus and milk after a. . . and bone. 2. Repeated oral administration of 20 or 200 mg/kg of NM441 to male rats did not affect hepatic drug-**metabolizing** enzyme activities. 3. In pregnant rats, the maximum concentration of radioactivity in the fetus was lower than that in the. . .

L4 ANSWER 4 OF 12 MEDLINE
AN 97259445 MEDLINE
DN 97259445 PubMed ID: 9105546
TI Pharmacokinetics of prulifloxacin. 1st communication: absorption, distribution and excretion in rats, dogs and monkeys after a single administration.
AU Okuyama Y; Momota K; Morino A
CS Research Laboratories, Nippon Shinyaku Co., Ltd., Kyoto, Japan.
SO ARZNEIMITTEL-FORSCHUNG, (1997 Mar) 47 (3) 276-84.
Journal code: 91U; 0372660. ISSN: 0004-4172.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199707

ED Entered STN: 19970721
Last Updated on STN: 19970721
Entered Medline: 19970707

AB The pharmacokinetics of prulifloxacin ((+/-)-6-fluoro-1-methyl-7-[4-(5-methyl-2-oxo-1,3-dioxolen-4-yl) methyl-1-piperazinyl]-4-oxo-4H-[1,3]thiazeto[3,2-a]**quinoline**-3-car boxylic acid. CAS 123447-62-1, NM441), a **quinolone** antibacterial prodrug, was investigated after i.v. (14C-NM394, CAS 112984-60-8) or oral (14C-NM441) administration to rats, dogs and monkeys. 1. 14C-NM441 was absorbed mainly from the upper small intestine and then **metabolized** to NM394 partly in the intestinal membrane but mainly in the portal blood and liver. Thus NM441 was not detected in the systemic circulation. 2. After i.v. administration of 14C-NM394 (5 mg/kg), the plasma concentration of radioactivity decreased biexponentially, and the elimination half-life in rats, dogs and monkeys was 4.2, 5.8 and 7.0 h, respectively. After oral administration of 14C-NM441 (20 mg/kg), the plasma concentration of radioactivity reached a maximum at 0.7-3.3 h, and thereafter decreased as observed after i.v. administration of 14C-NM394. An effect of food on the absorption of NM441 was found. No clear sex-related differences were observed in the plasma concentration profiles of rats. 3. The concentration of radioactivity in most tissues of rats reached a maximum within 1 h after oral administration of 14C-NM441 and thereafter decreased along with the plasma concentration. At 0.5 h, the radioactivity concentrations were highest in the liver and kidney, moderately high in the spleen, pancreas, lung and mandibular gland and extremely low in the cerebrum and cerebellum. 4. The radioactivity in the excreta collected over a 96-h period was 96-98% of the oral dose (urine, 22-32%; feces, 64-75%) in rats, dogs and monkeys, 35% of the radioactivity administered was excreted in the bile of rats during a 48-h period after oral administration, and only a small portion of the biliary radioactivity was reabsorbed. 5. The proportion of 14C-NM394 that bound to serum proteins in vitro in rats, dogs, monkeys and humans was 41-59% in a concentration range of 0.1-10 micrograms/ml.

AB The pharmacokinetics of prulifloxacin ((+/-)-6-fluoro-1-methyl-7-[4-(5-methyl-2-oxo-1,3-dioxolen-4-yl) methyl-1-piperazinyl]-4-oxo-4H-[1,3]thiazeto[3,2-a]**quinoline**-3-car boxylic acid. CAS 123447-62-1, NM441), a **quinolone** antibacterial prodrug, was investigated after i.v. (14C-NM394, CAS 112984-60-8) or oral (14C-NM441) administration to rats, dogs and monkeys. 1. 14C-NM441 was absorbed mainly from the upper small intestine and then **metabolized** to NM394 partly in the intestinal membrane but mainly in the portal blood and liver. Thus NM441 was not detected. . .

L4 ANSWER 5 OF 12 MEDLINE
AN 95142571 MEDLINE
DN 95142571 PubMed ID: 7840564
TI Possible intermolecular interaction between quinolones and biphenylacetic acid inhibits gamma-aminobutyric acid receptor sites.
AU Akahane K; Kimura Y; Tsutomi Y; Hayakawa I
CS Exploratory Research Laboratories I, Daiichi Pharmaceutical Co., Tokyo, Japan.
SO ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1994 Oct) 38 (10) 2323-9.

Journal code: 6HK; 0315061. ISSN: 0066-4804.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199503
ED Entered STN: 19950314
Last Updated on STN: 19950314
Entered Medline: 19950302

AB The combination of some new **quinolone** antibacterial agents with 4-biphenylacetic acid (BPAA), a **metabolite** of fenbufen, is known to specifically induce functional blockade of the gamma-aminobutyric acid (GABA) receptors. The mechanisms of these drug interactions were further examined. Scatchard analysis of [3H]muscimol binding to rat brain plasma membranes in the presence of enoxacin and BPAA revealed that a significant decrease in the number of muscimol binding sites was produced without affecting the affinity of binding to the receptors. In the presence of norfloxacin, BPAA inhibited muscimol binding the most potently of the six BPAA-related compounds tested. Fenbufen and 9,10-dihydro-gamma-oxo-2-phenanthrenebutyric acid also inhibited the binding, and 4-biphenylcarboxylic acid and methyl 4-biphenylacetate inhibited it slightly, but 3-benzoylpropionic acid exhibited no competitive inhibition.
Accordingly, hybrid molecules of norfloxacin and BPAA were synthesized for stereochemical analysis of these drug interactions. A hybrid with a -CONH(CH2)3- chain between norfloxacin and BPAA (flexible structure) inhibited muscimol binding, and intracisternal injection of this hybrid caused clonic convulsions in mice more potently than the combination of norfloxacin and BPAA did. In contrast, a hybrid linked by -CONH- (stretched structure) showed almost no such inhibitory effect. 1H NMR analysis indicated the presence of intramolecular attraction at the **quinoline** ring of the hybrid exhibiting the antagonistic activity. These results suggest the possibility that **quinolones** and BPAA interact with the GABA receptor at nearby sites and that the binding affinity of **quinolones** to the GABA receptors is largely enhanced by the intermolecular interaction with BPAA.
AB The combination of some new **quinolone** antibacterial agents with 4-biphenylacetic acid (BPAA), a **metabolite** of fenbufen, is known to specifically induce functional blockade of the gamma-aminobutyric acid (GABA) receptors. The mechanisms of these drug. . . -CONH- (stretched structure) showed almost no such inhibitory effect. 1H NMR analysis indicated the presence of intramolecular attraction at the **quinoline** ring of the hybrid exhibiting the antagonistic activity. These results suggest the possibility that **quinolones** and BPAA interact with the GABA receptor at nearby sites and that the binding affinity of **quinolones** to the GABA receptors is largely enhanced by the intermolecular interaction with BPAA.

L4 ANSWER 6 OF 12 MEDLINE
AN 93267575 MEDLINE
DN 93267575 PubMed ID: 8388467
TI Quinolone antimicrobial agents substituted with morpholines at the 7-position. Syntheses and structure-activity relationships.
AU Araki K; Kuroda T; Uemori S; Moriguchi A; Ikeda Y; Hirayama F; Yokoyama Y;

Iwao E; Yakushiji T
CS Research Laboratories, Yoshitomi Pharmaceutical Industries Ltd, Japan.
SO JOURNAL OF MEDICINAL CHEMISTRY, (1993 May 14) 36 (10) 1356-63.
Journal code: J0F; 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199306
ED Entered STN: 19930702
Last Updated on STN: 19930702
Entered Medline: 19930622
AB A series of novel 7-substituted 1-cyclopropyl-6,8-difluoro-1, 4-dihydro-4-oxo-3-**quinolinecarboxylic** acids have been prepared and tested for antibacterial activities and for convulsive activities in combination with nonsteroidal antiinflammatory drug. Structure-activity relationships revealed that 7-(2-(aminomethyl)morpholino) derivative 28 had a better Gram-positive activity than the reference **quinolones**, such as ciprofloxacin, norfloxacin, and ofloxacin. Its Gram-negative activity was equipotent with those of norfloxacin and ofloxacin but was inferior to that of ciprofloxacin. In mouse systemic infection models, 28 showed an excellent therapeutic efficacy which might result from the potent antibacterial activity and suitable physicochemical properties. Convulsive activities of 7-morpholino derivatives in combination with nonsteroidal antiinflammatory drug fenbufen or its **metabolite** biphenylacetic acid markedly diminished as compared to those of 7-piperazino derivatives in the electrophysiological, biochemical, and behavioral experiments. These results suggest that 28 (Y-26611) is a novel **quinolone** with reduced neurotoxic excitatory adverse reaction.
AB A series of novel 7-substituted 1-cyclopropyl-6,8-difluoro-1, 4-dihydro-4-oxo-3-**quinolinecarboxylic** acids have been prepared and tested for antibacterial activities and for convulsive activities in combination with nonsteroidal antiinflammatory drug. Structure-activity relationships revealed that 7-(2-(aminomethyl)morpholino) derivative 28 had a better Gram-positive activity than the reference **quinolones**, such as ciprofloxacin, norfloxacin, and ofloxacin. Its Gram-negative activity was equipotent with those of norfloxacin and ofloxacin but was inferior. . . antibacterial activity and suitable physicochemical properties. Convulsive activities of 7-morpholino derivatives in combination with nonsteroidal antiinflammatory drug fenbufen or its **metabolite** biphenylacetic acid markedly diminished as compared to those of 7-piperazino derivatives in the electrophysiological, biochemical, and behavioral experiments. These results suggest that 28 (Y-26611) is a novel **quinolone** with reduced neurotoxic excitatory adverse reaction.

L4 ANSWER 7 OF 12 MEDLINE
AN 93156699 MEDLINE
DN 93156699 PubMed ID: 8429824
TI Quinolone antibacterial agents: relationship between structure and in vitro inhibition of the human cytochrome P450 isoform CYP1A2.
AU Fuhr U; Strobl G; Manaut F; Anders E M; Sorgel F; Lopez-de-Brinas E; Chu D
T; Pernet A G; Mahr G; Sanz F; +
CS Department of Clinical Pharmacology, University Hospital Frankfurt,

Germany.
SO MOLECULAR PHARMACOLOGY, (1993 Feb) 43 (2) 191-9.
Journal code: NGR; 0035623. ISSN: 0026-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199303
ED Entered STN: 19930326
Last Updated on STN: 19970203
Entered Medline: 19930309

AB The inhibitory effect of 44 **quinolone** antibacterials and derivatives (common structure, 4-oxoquinoline-3-carboxylic acid) on cytochrome P450 isoform CYP1A2 activity was tested using human liver microsomes and caffeine 3-demethylation as a specific test system for this enzyme. By direct comparison of molecules differing structurally in only one position, the following structure-activity relationships were found. 3'-Oxo derivatives had a reduced or similar activity and M1 **metabolites** (cleavage of piperazinyl substituent) had a greater inhibitory activity, compared with the parent molecule. Alkylation of the 7-piperazinyl substituent resulted in a reduced inhibitory potency. Naphthyridines with an unsubstituted piperazinyl group at position 7 displayed a greater inhibitory potency than did corresponding **quinoline** derivatives. Derivatives with a fluorine substitution at position 8 had only a minor effect. Molecular modeling studies with inhibitors and caffeine showed that it is possible to explain the potency of the **quinolones** to inhibit CYP1A2 on a molecular level. The keto group, the carboxylate group, and the core nitrogen at position 1 are likely to be the most important groups for binding to the active site of CYP1A2, because the molecular electrostatic potential of all inhibitors is very similar to that of caffeine in these regions. The presence of a piperazinyl substituent, however, seems to be no prerequisite for inhibitory potency. Finally, an equation to estimate the potency to inhibit CYP1A2 was developed by quantitative structure-activity relationship analysis.

AB The inhibitory effect of 44 **quinolone** antibacterials and derivatives (common structure, 4-oxoquinoline-3-carboxylic acid) on cytochrome P450 isoform CYP1A2 activity was tested using human liver microsomes and. . . in only one position, the following structure-activity relationships were found. 3'-Oxo derivatives had a reduced or similar activity and M1 **metabolites** (cleavage of piperazinyl substituent) had a greater inhibitory activity, compared with the parent molecule. Alkylation of the 7-piperazinyl substituent resulted. . . reduced inhibitory potency. Naphthyridines with an unsubstituted piperazinyl group at position 7 displayed a greater inhibitory potency than did corresponding **quinoline** derivatives. Derivatives with a fluorine substitution at position 8 had only a minor effect. Molecular modeling studies with inhibitors and caffeine showed that it is possible to explain the potency of the **quinolones** to inhibit CYP1A2 on a molecular level. The keto group, the carboxylate group, and the core nitrogen at position 1. . .

L4 ANSWER 8 OF 12 MEDLINE
AN 93154213 MEDLINE
DN 93154213 PubMed ID: 1362942
TI Role of guinea pig and rabbit hepatic aldehyde oxidase in oxidative in vitro metabolism of cinchona antimalarials.
AU Beedham C; al-Tayib Y; Smith J A
CS School of Pharmacy, University of Bradford, UK.
SO DRUG METABOLISM AND DISPOSITION, (1992 Nov-Dec) 20 (6) 889-95.
Journal code: EBR; 9421550. ISSN: 0090-9556.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199303
ED Entered STN: 19930326
Last Updated on STN: 19950206
Entered Medline: 19930308
AB Cinchona alkaloids (quinine, quinidine, cinchonine, and cinchonidine) were
incubated with partially purified aldehyde oxidase from rabbit or guinea pig liver. Reversed-phase HPLC methods were developed to separate the oxidation products from the parent drugs, and the **metabolites** were identified on the basis of their infrared and mass spectral characteristics. All four alkaloids were oxidized at carbon 2 of the **quinoline** ring to give the corresponding lactams. In addition, the dihydro contaminants of the cinchona alkaloids were also **metabolized** by aldehyde oxidase to the 2-**quinolone** derivatives. Kinetic constants for the oxidation reactions were determined
spectrophotometrically and showed that these substrates have a low affinity (KM values of around 10(-5) M) for hepatic aldehyde oxidase, coupled with a relatively low oxidation rate. However, the overall efficiency of the enzyme (Vmax/KM) toward this group of compounds indicates that in vivo biotransformation by aldehyde oxidase will be a significant pathway. Microsomal **metabolites** were also isolated from quinine and quinidine incubations with rabbit or guinea pig liver fractions. 3-Hydroxyquinine (quinidine) and O-desmethylquinine (quinidine)
were identified in microsomal and 10,000g supernatant extracts from quinine and quinidine, respectively. Oxidation of quinine via aldehyde oxidase appeared to be the predominant pathway in rabbit 10,000g fractions, because 2'-quininone was the major **metabolite** under these conditions with lower concentrations of the microsomal **metabolites** produced along with a dioxygenated derivative thought to be 3-hydroxy-2'-quininone.
AB . . . or guinea pig liver. Reversed-phase HPLC methods were developed to separate the oxidation products from the parent drugs, and the **metabolites** were identified on the basis of their infrared and mass spectral characteristics. All four alkaloids were oxidized at carbon 2 of the **quinoline** ring to give the corresponding lactams. In addition, the dihydro contaminants of the cinchona alkaloids were also **metabolized** by aldehyde oxidase to the 2-**quinolone** derivatives. Kinetic constants for the oxidation reactions were determined
spectrophotometrically and showed that these substrates have a low affinity (KM. . . (Vmax/KM) toward this group of compounds indicates

that in vivo biotransformation by aldehyde oxidase will be a significant pathway. Microsomal **metabolites** were also isolated from quinine and quinidine incubations with rabbit or guinea pig liver fractions. 3-Hydroxyquinine (quinidine) and O-desmethylquinine (quinidine). . . of
quinine via aldehyde oxidase appeared to be the predominant pathway in rabbit 10,000g fractions, because 2'-quininone was the major **metabolite** under these conditions with lower concentrations of the microsomal **metabolites** produced along with a dioxygenated derivative thought to be 3-hydroxy-2'-quininone.

L4 ANSWER 9 OF 12 MEDLINE
AN 92191341 MEDLINE
DN 92191341 PubMed ID: 1666026
TI Pharmacological properties of galenical preparation. XV. Pharmacokinetics study of evocarpine and its metabolite in rats.
AU Kano Y; Chen X F; Kanemaki S; Zong Q; Komatsu K
CS Hokkaido Institute of Pharmaceutical Sciences, Otaru, Japan.
SO CHEMICAL AND PHARMACEUTICAL BULLETIN, (1991 Nov) 39 (11) 3064-6.
Journal code: CZP; 0377775. ISSN: 0009-2363.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199204
ED Entered STN: 19920509
Last Updated on STN: 19920509
Entered Medline: 19920420
AB It is known that when methanol extract of Evodia fruit is orally administered, 5-(1,4-dihydro-1-methyl-4-oxo-2-**quinolin**-2-yl) pentanoic acid (EVCA) is excreated as a matabolite in rat urine. In this study, we separated Evodia fruit extract into major alkaloids administered
each alkaloid individually to male Wistar rats. Consequently, it was demonstrated that the original substance of the **metabolite** are evocarpine and its analogues, dihydroevocarpine and 1-methyl-2-undecenyl-4(1H)-**quinolone**. Investigation of a blood sample after oral administration of evocarpine by high performance liquid chromatography confirmed that the substance was absorbed without alteration. Pharmacokinetics of evocarpine after intravenous injection was expressed in a one-compartment model, showing a linear elimination of plasma evocarpine up to a dosage of 75 mg/kg. Total plasma clearance (CL), volume
of distribution (Vd), and half-life (T1/2) of evocarpine were 60 ml/min.kg, 3.21/kg and 0.6 h-1, respectively. **Metabolic** ratio of evocarpine into EVCA after intravenous injection was 15.4%, and absorption
ratio of the unaltered compound calculated from the levels of AUC after oral administration and intravenous injection was 4.7%. In this paper, it is shown that evocarpine is absorbed amount 100% when it is administered orally.
AB It is known that when methanol extract of Evodia fruit is orally administered, 5-(1,4-dihydro-1-methyl-4-oxo-2-**quinolin**-2-yl) pentanoic acid (EVCA) is excreated as a matabolite in rat urine. In this study, we separated Evodia fruit extract into. . . major alkaloids administered each alkaloid individually to male Wistar rats. Consequently,

it was demonstrated that the original substance of the **metabolite** are evocarpine and its analogues, dihydroevocarpine and 1-methyl-2-undecenyl-4(1H)-**quinolone**. Investigation of a blood sample after oral administration of evocarpine by high performance liquid chromatography confirmed that the substance was. . . plasma clearance (CL), volume of distribution (Vd), and half-life (T1/2) of evocarpine were 60 ml/min.kg, 3.21/kg and 0.6 h-1, respectively. **Metabolic** ratio of evocarpine into EVCA after intravenous injection was 15.4%, and absorption ratio of the unaltered compound calculated from the. . .

L4 ANSWER 10 OF 12 MEDLINE
AN 90210446 MEDLINE
DN 90210446 PubMed ID: 2698608
TI Recent acquisitions on chemotherapy and chemoprophylaxis of malaria.
AU Onori E; Majori G
SO ANNALI DELL ISTITUTO SUPERIORE DI SANITA, (1989) 25 (4) 659-73. Ref: 129
Journal code: 5BP; 7502520. ISSN: 0021-2571.
CY Italy
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199005
ED Entered STN: 19900601
Last Updated on STN: 19900601
Entered Medline: 19900501
AB The most recent acquisitions on chemotherapy and chemoprophylaxis of malaria are reviewed. With regard to chemotherapy, candidate antimalarial compounds have been divided into four groups, according to their stages of development. Mefloquine and the combination of mefloquine with sulfadoxine/pyrimethamine belong to the first group: they have completed clinical trials and have been registered in several countries for routine clinical use. The second group is characterized by chemical compounds which are in an advanced stage of development, including clinical trials. The compounds considered in this group are: a) the 9-phenanthrenemethanols, among which halofantrine is the most promising one; b) the sesquiterpene lactones such as Qinghaosu, artemether, artesunate, artesunic acid and arteether which must be further tested in order to find more effective drug regimens capable of eliminating recrudescences and for the completion of toxicity studies; c) pyronaridine, which appears to be a promising antimalarial, effective also against chloroquine-resistant P. falciparum, but still requiring further investigations on resistance and cross-resistance, as well as its pharmacokinetics, tolerability and bioavailability; d) enpiroline, another promising compound, which needs to be further studied in Phase II and Phase III investigations with naturally acquired malaria. The third group is composed of seven chemical classes of

compounds that are in an advanced pre-clinical development, namely: the 4-aminoquinolines, such as dabechin, piperaquine, hydroxypiperaquine, tripiperaquine, dichlor-quinazine and the Mannich base compounds, the 8-aminoquinolines, the 4-**quinolinemethanols**, the **quinolones**, the naphthoquinones, the quinazolines and the dihydrotriazines. Among the many antimalarial compounds of interest, which can be considered at the moment as leads for further studies, only the acridandione derivatives such as floxacrine, the antibiotics, antifungal agents or their **metabolites**, plant substances such as Yingzhaosu A and quassinoids have been mentioned. Malaria chemoprophylaxis, especially in chloroquine-resistant P. falciparum areas, has become a real problem. The attempts to secure protection under these circumstances with the utilization of amodiaquine, the combination of sulfadoxine/pyrimethamine (Fansidar), sulfalene/pyrimethamine (Metakelfin), of pyrimethamine/dapsone (Maloprim), with or without chloroquine, had to be abandoned or to be used with caution in view of the severe complications following the weekly administration of these drugs. The combination of chloroquine with proguanil or chlorproguanil, which could be recommended on theoretical bases, did not meet the expectations when tested in the field. (ABSTRACT TRUNCATED AT 400 WORDS)

AB . . . pre-clinical development, namely: the 4-aminoquinolines, such as dabechin, piperaquine, hydroxypiperaquine, tripiperaquine, dichlor-quinazine and the Mannich base compounds, the 8-aminoquinolines, the 4-**quinolinemethanols**, the **quinolones**, the naphthoquinones, the quinazolines and the dihydrotriazines. Among the many antimalarial compounds of interest, which can be considered at the moment as leads for further studies, only the acridandione derivatives such as floxacrine, the antibiotics, antifungal agents or their **metabolites**, plant substances such as Yingzhaosu A and quassinoids have been mentioned. Malaria chemoprophylaxis, especially in chloroquine-resistant P. falciparum areas, has. . .

L4 ANSWER 11 OF 12 MEDLINE
AN 90079742 MEDLINE
DN 90079742 PubMed ID: 2593082
TI Kinetic interaction between theophylline and a newly developed quinolone, NY-198.
AU Kuzuya T; Takagi K; Apichartpichean R; Muraoka I; Nadai M; Hasegawa T
CS Department of Hospital Pharmacy, Nagoya University, School of Medicine, Japan.
SO JOURNAL OF PHARMACOBIO-DYNAMICS, (1989 Jul) 12 (7) 405-9.
Journal code: JNC; 7901854. ISSN: 0386-846X.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199001
ED Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19900125
AB The effect of a newly developed **quinolone**, NY-198, on the pharmacokinetics and **metabolism** of theophylline was investigated

under steady-state conditions in six male healthy volunteers, in a crossover fashion. A sustained-release theophylline formulation (200 mg twice daily at 12 h intervals) was received as monotherapy or coadministration with NY-198 (200 mg twice daily at 12 h intervals). No significant change in the pharmacokinetic parameters of theophylline was observed during coadministration of NY-198. No significant change in urinary excretion of theophylline and its **metabolites** was also observed. These findings indicate that NY-198 does not influence the pharmacokinetics of theophylline and we can suggest that **quinoline** derivatives have less effect on theophylline disposition than 1,8-naphthyridine derivatives among **quinolones**.

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L4 ANSWER 12 OF 12 MEDLINE
AN 87034119 MEDLINE
DN 87034119 PubMed ID: 3095363
TI High-performance liquid chromatographic determination of 6,8-difluoro-1-(2-fluoroethyl)-1,4- dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid and its metabolites in laboratory animals.
AU Kusajima H; Ooie T; Kawahara F; Uchida H
SO JOURNAL OF CHROMATOGRAPHY, (1986 Aug 22) 381 (1) 137-48.
Journal code: HQF; 0427043. ISSN: 0021-9673.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198611
ED Entered STN: 19900302
Last Updated on STN: 19900302
Entered Medline: 19861124

AB A simple, sensitive and specific high-performance liquid chromatographic method for a new **quinolone** antimicrobial agent, 6,8-difluoro-1-(2-fluoroethyl)-1,4- dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-**quinolinecarboxylic** acid (AM-833, I), and its **metabolites** in serum and urine has been developed for their simultaneous determination. This method is based on ion-pair extraction and separation by ion-pair reversed-phase chromatography with ultraviolet or fluorescence detection. The major **metabolites** in the serum and urine of mice, rats, dogs and monkeys were N-desmethyl I (compound II) and I N-oxide (compound III). Rabbit serum and urine contained N-desmethyl-3-oxo I (compound IV), 3-oxo I (compound V) and N-desmethyl-4-formyl I (compound VI) in addition to compounds I, II and III. Unchanged drug accounted for 80-90% of total serum concentrations in

mice and more than 90% in rats, dogs and monkeys up to 6 h after dosing, whereas the fraction of compound I in rabbits was 34-67%. Unchanged drug was the most predominant in the urine of mice, rats, dogs and monkeys, whereas compound II was the most abundant in rabbit urine. Although rabbits and monkeys excreted 70-80% of dose in three-day urine, the total urinary excretion of mice, rats and dogs was relatively low, 40-50% of oral dose. The fraction of compound I in total urinary excretion was 63, 73, 27, 55 and 78% in mice, rats, rabbits, dogs and monkeys, respectively.

These results suggest that there is a species difference in the **metabolism** and excretion pathway of compound I.

AB A simple, sensitive and specific high-performance liquid chromatographic method for a new **quinolone** antimicrobial agent, 6,8-difluoro-1-(2-fluoroethyl)-1,4- dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-**quinolinecarboxylic** acid (AM-833, I), and its **metabolites** in serum and urine has been developed for their simultaneous determination. This method is based on ion-pair extraction and separation by ion-pair reversed-phase chromatography with ultraviolet or fluorescence detection. The major **metabolites** in the serum and urine of mice, rats, dogs and monkeys were N-desmethyl I (compound II)

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